

REMARKS

Claims 1-35 are pending in the present application. Claims 15, 16, 31 and 32 have been withdrawn from consideration. All of the claims under consideration have been rejected either under 35 U.S.C. §112 as indefinite or as obvious under 35 U.S.C. §103. Applicants respectfully traverse these rejections.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

I. Information Disclosure Statement

The initialed PTO form 1449 accompanying the Office Action indicated that Klagsburn, M., "Large Scale Preparation of Chondrocytes," Methods Enzymol., Vol. 58, pp. 560-564, 1979; published by Academic Press, Inc. was not considered and was noted as an "incomplete reference." Enclosed herewith is a full copy of this reference. Accordingly, applicants respectfully request the Examiner consider this reference and make it of record in the present application.

II. Claim Rejection – 35 U.S.C. §112

In the Office Action, claims 1, 17 and their dependents were rejected "because it is unclear what 'effects' are being determined. Applicant fails to specifically point out what effects the method is determining, as there is no recitation of a determining step. For example, there is no defined limitation wherein a particular result indicates an 'effect' or not. Moreover, it is unclear what effect, if any, must occur to practice the claimed invention." Applicants respectfully traverse this rejection because "effect" is being used in the claims in accord with its plain and ordinary meaning of "something that inevitably follows an antecedent (as a cause or agent)[.]" MERRIAM WEBSTER'S COLLEGiate DICTIONARY 367 (Tenth Ed. 1997)(copy enclosed). Applicants also note that although there is no step that recites "determining," (C) recites

“measuring...” Moreover, the skilled artisan would clearly recognize when a test agent has an effect on a cell or tissue. For example, one skilled could perform numerous analytical tests common in the art to measure cell viability, matrix production, matrix composition, etc. The nature of the effect has not been specified in the present claims as the specific effect observed is not critical to the present invention, and, in fact, no effect is required to occur in order to practice the claimed invention.

Claims 1, 17 and their dependents were also rejected “for reciting both ‘tissue engineered cartilage matrix’ and ‘engineered cartilage tissue’ because it is unclear if applicant is using the term interchangeably.” Applicants respectfully traverse this rejection because the phrase “tissue engineered cartilage matrix” is used only in the preamble of claims 1, 15 and 17, whereas the phrase “engineered cartilage tissue” is used only in the body of the claims. Accordingly, there is no overlap in usage of the phrases that would confuse one skilled in the art. Additionally, the preambles of claims 1, 15 and 17 “merely states... the purpose or intended use of the invention, rather than any distinct definition of any of the claims invention’s limitations, [and, accordingly,] the preamble is not considered a limitation and is of no significance to claim construction.” MPEP §2111.02.

Claims 1, 17 and their dependents were also rejected as “indefinite because while the method is drawn to determining effects on an engineered cartilage tissue (ECT), step (B) allows for the determining step to occur on isolated chondrogenic cells before they have formed into the ECT. It is unclear how one could determine the effects of an agent on an ECT by contacting cells that have yet to form an ECT.” Applicants respectfully submit this rejection is based on a misunderstanding of the present claims and the art. As above, the preamble does not limit the claimed invention. Instead, the body of the claim clearly recites “measuring the effect the one or more test agents has on the contacted cells.” One skilled in the art would understand this as covering all possible cells and stages of cartilage formation clearly recited in (B), which does not involve any determination but only contacting the test agent with the desired cells. The skilled artisan would also clearly understand how to determine the effect a test agent has on chondrogenic cells that have yet to form an ECT, which can provide important information regarding cartilage formation. For example, such a determination could be made by comparing

the effect of a sample using a test agent against a control experiment in which no test agent is used, such as discussed in paragraph [0043] of the present application.

Claims 11 and 27 were rejected “because it is unclear if step (C) rather comprises enzymatically degrading the ECT, or further comprises enzymatically degrading ECT.” Applicants are confused by this rejection as claims 11 and 27 use clear language and simply recite “wherein step (C) comprises enzymatically degrading the engineered cartilage tissue.” Accordingly, the skilled artisan would understand that (C) could further comprise enzymatically degrading the cartilage tissue, if other steps are used to measure the effect of the test agent, but (C) does not require additional steps or assays if the enzymatic degradation of the of the cartilage tissue provides an adequate measure of the effect of the test agent.

Claims 14 and 33 were rejected as “indefinite because it is unclear how one ‘identifies’ a desirable test agent, as there is no specific property required to make it desirable.” Applicants are confused by this rejection because the word “identifying” is being used with its plain and ordinary meaning of “to establish the identity of[.]” MERRIAM WEBSTER’S COLLEGiate DICTIONARY 575 (Tenth Ed. 1997)(copy enclosed). One skilled in the art that would readily understand how to identify a test agent having a desired property and that the specific property or properties that make a test agent desirable is variable. For example, if a test agent helped produce a cartilage matrix faster, and faster matrix production is a desired characteristic, the agent that provides this effect can be identified by the present methods and produced.

Because the claims “apprise[] one of ordinary skill in the art of [their] scope and, therefore, serve[] the notice function required by 35 U.S.C. §112, second paragraph” applicants respectfully request the Examiner withdraw these rejections. MPEP §2173.02.

III. Claim Rejections – 35 U.S.C. §103

In the Office Action, claims 1-8, 10, 14, 17-24, 26, 29-30 and 33 were “rejected under 35 U.S.C. 103(a) as being unpatentable over Kai *et al.* (JP 2001 089390 A) in view of Masuda *et al.* (US 6197061 B1).” Applicants respectfully submit that the Examiner is reading

more into the Kai *et al.* than is warranted from the short English translation of the abstract of Kai *et al.* provided with the present Office Action.

As stated in the MPEP “When applying 35 U.S.C. 103, the following tenet[] of patent law must be adhered to:

The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination[.]” MPEP §2141. Yet, neither Kai *et al.* nor Masuda *et al.* provide a suggestion or motivation to combine their teachings. The Office Action attempts to overcome this deficiency by stating that “one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Kai *et al.* via the methods of Masuda[.]” However, no commonality between the culture methods of Kai *et al.* and Masuda *et al.* are discussed in the Office action. In fact, the portion of Kai *et al.* makes no reference to culture conditions. It is well known in the art that the conditions in which cells are cultured has a dramatic effect on cell fate. Accordingly, it is unlikely that the culture methods of Kai *et al.* can be suitably modified by those taught by Masuda *et al.* absent very similar methodology. Moreover, the differences in the culture conditions between the references are divergent because the references deal with different cell subsets. Kai *et al.* are only concerned with isolated chondrocytes and their ability to form chondrons whereas Masuda *et al.* are directed to the production of a cohesive cartilage tissue, not individual chondrocyte cells. Finally, neither reference suggests why the teachings of Kai *et al.* should be altered using the culture conditions of Masuda *et al.* as Kai *et al.* disclose that their method is fully suited for its intended purpose. Applicants also respectfully submit that this rejection is merely a hindsight reconstruction of the present invention in which two references have been combined that appear to teach all of the elements of the present claims. Accordingly, the combination of Kai *et al.* and Masuda *et al.* cannot state a proper *prima facie* case of obviousness and applicants respectfully request the Examiner withdraw this rejection.

Claims 1-10, 14, 17-26, 33 and 35 were “rejected under 35 U.S.C. 103(a) as being unpatentable over Purchio *et al.* (US 5902741) in view of Masuda.” As above, there is no motivation in either of the references or the art to combine the teachings of Purchio *et al.* with

Masuda *et al.* Again, the Office Action makes the unsupported statement that “one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Purchio via the methods of Masuda because it was a known method for culturing cartilage tissues.” However, no commonality between the culture methods of Purchio *et al.* and Masuda *et al.* are discussed in the Office action. This statement is also akin to saying that all known methods are available in all combinations in the art and not only ignores the disparate teachings of the references but also the legal standard for stating a *prima facie* case of obviousness. Even if “the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.” MPEP §2143.01 (emphasis added).

To the skilled artisan, Purchio *et al.* appear to teach an acceptable method for culturing a cartilage tissue and determining the effect of test agents on the tissue. As such, one skilled in the art would have no motivation to complicate the method disclosed by Purchio *et al.* by modifying the technique along the lines of Masuda *et al.* In fact, the skilled artisan would recognize that Purchio *et al.* and Masuda *et al.* teach in different directions and that modifying Purchio *et al.* would render the references unsatisfactory for its intended purpose. For example, Purchio *et al.* is directed solely to cells that “are inoculated and grown on three-dimensional frameworks or biodegradable scaffolds.” Column 6, lines 12-13. In contrast, Masuda *et al.* is directed to engineered cartilage tissue produced on a “semipermeable membrane.” Column 4, line 42. This distinction is not an inconsequential one because in Purchio *et al.* the “cells and connective tissue proteins secreted by the stromal cells attach to and substantially envelope the three dimensional framework or construct[.]” Column 6, lines 21-23 (emphasis added). Thus, the three-dimensional framework or scaffold becomes an integral part of the cultured tissue making removal of the tissue of Purchio *et al.* from the framework impossible. The semipermeable membrane of Masuda *et al.* can be removed from the cartilage tissue.

Accordingly, because the “proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose then there is no suggestion or motivation to make the proposed modification” and the “proposed modification or combination of the prior art change[s] the principle of operation of the prior art invention being modified, then the teachings

of the references are not sufficient to render the claims *prima facie* obvious.” MPEP §2143.02. Therefore, applicants respectfully request the Examiner withdraw this rejection.

Claims 1-12, 14, 17-28 and 33 were “rejected under 35 U.S.C. 103(a) as being unpatentable over Hunziker (US 5368858 A) in view of Masuda.” Hunziker is cited for teaching “a method wherein engineered cartilage is exposed to therapeutic test agents to observe its effects on the cartilage (example 1).” Applicants respectfully submit that this statement is based on a misunderstanding of Hunziker. Example 1 of Hunziker merely teaches “enzyme testing for proteoglycan removal.” Column 13, line 44. Proteolytic enzymes and their effects on cartilage tissue were known in the art and as such do not constitute a test agent as defined by the present invention. See, for example, paragraph [0040] of the present application. Nowhere do Hunziker disclose the use of a test agent in Example 1. In fact, Hunziker *et al.* do not even deal with the production of cartilage tissues *ex vivo*. Hunziker *et al.* merely disclose implantation of a non-cartilage matrix into a cartilage defect containing known compounds. See, e.g. column 3, lines 45-60. After implantation, “repair cells are free to populate the matirx and proliferate in order to fill to volume of the defect that the matrix occupies.” Column 6, lines 4-42. As such, Hunziker and Masuda *et al.*, either alone or in combination, fail to teach or suggest all of the elements of the rejected claims. Therefore, this combination of references cannot state a *prima facie* case of obviousness. MPEP §2143. This rejection must also fail for the reasons discussed above because one skilled in the art simply could not modify the cartilage culture of Hunziker with Masuda *et al.* because the cartilage culture of Hunziker is non-existent. Accordingly, applicants respectfully request the Examiner withdraw this rejection.

Claim 1-8, 17-24, 29-30 and 35 were also “rejected under 35 U.S.C. 103(a) as being unpatentable over Saito (July 1999) in view of Masuda *et al.*” Saito *et al.* are cited for teaching “culturing cartilage in multi well plates in the presence of IL-1 alpha, wherein the effects of test agents are measured (p. 727).” Yet again, there is no motivation or suggestion to combine these references. Saito *et al.* use cartilage explants obtained directly from animals for their testing whereas Masuda *et al.* is directed to an engineered, man made cartilage tissue. Although the Office Action states “one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Saito via the methods of Masuda

because it was a known method for culturing cartilage tissues" it is not apparent how the skilled artisan could even combine the teachings of Saito *et al.* and Masuda *et al.* Saito *et al.* use cartilage explants obtained directly from animals. Masuda *et al.*'s disparate methods are directed to the production of a man made cartilage tissue. This begs the question how, or why, the skilled artisan could, or would, culture a cartilage explant to obtain an artificial cartilage tissue. Performing such a method would require destruction of the cartilage explant and many additional processing steps which would completely change the principle of operation disclosed by Saito *et al.* Moreover, the present invention specifically overcomes the problems associated with the cartilage explants of Saito *et al.* because "the intra- and intervariability of the results [using cartilage explants] are often unacceptably large. Cartilage explants are also undesirable because it is difficult to obtain large amounts of human cartilage tissue and researchers must follow special procedures in order to comply with ethical research requirements." Paragraph [0005] of the present application. Accordingly, applicants respectfully request the Examiner withdraw this rejection.

Claims 1-11, 17-27 and 29-30 were also "rejected under 35 U.S.C. 103(a) as being unpatentable over Huch *et al.* (1997) in view of Masuda." This rejection must also fail for the reasons discussed above, and, in particular, those relating to the combination of Kai *et al.* and Masuda *et al.* Huch *et al.* is directed to testing compounds on individual chondrocytes. In contrast, Masuda *et al.* teaches the production of a cohesive cartilage tissue. The differences in the culture conditions between the references are also divergent because the references deal with different cell subsets and maturation levels. Finally, neither reference suggests why the teachings of Huch *et al.* should be altered using the culture conditions of Masuda *et al.* as Huch *et al.* disclose that their method is fully suited for its intended purpose. As stated in the MPEP "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP §2143.01. Accordingly, the combination of Huch *et al.* and Masuda *et al.* cannot state a proper *prima facie* case of obviousness and applicants respectfully request the Examiner withdraw this rejection.

Finally, claims 1-8, 10, 14, 17-24, 26 and 33 were "rejected under 35 U.S.C. 103(a) as being unpatentable over Lansbury *et al.* (WO 94/28889) in view of Masuda." This

combination also does not state a *prima facie* case of obviousness for the reasons discussed above, e.g., there is no motivation to combine the references and the references teach away from their combination because Lansbury *et al.* only deal with the culture of chondrocytes, not the production of a whole, cohesive cartilage matrix. Therefore, applicants also respectfully request the Examiner withdraw this rejection.

CONCLUSION

In view of the above remarks, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

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